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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,471	09/01/2006	Elliot Ehrich	2685.3002 US	4421

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EXAMINER	
POLANSKY, GREGG	
ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,471	EHRICH ET AL.	
	Examiner	Art Unit	
	GREGG POLANSKY	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-8,10-16 and 18-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-8,10-16 and 18-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/16/2008 & 10/21/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicants' response, filed 10/21/2008, to the Office Action mailed 4/22/2008 is acknowledged. Applicants amended the Specification and presented arguments in response to the Office Action.

2. Applicants' Information Disclosure Statements, filed 5/16/2008 and 4/28/2008, are acknowledged and have been reviewed.

3. Applicants' arguments have been fully considered and they are persuasive in part. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

4. Claims 1, 2, 4-8, 10-16, and 18-28 are pending and presently under consideration.

Claim Rejections - 35 USC § 102

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 1, 4, 5, and 22-26 rejected are under 35 U.S.C. 102(b) as being anticipated by Freund et al. (U.S. Patent Application Pub. No. 2001/0008632).

Freund et al. teach aqueous aerosols of *inter alia* anticholinergic agents, including trospium chloride and ipratropium bromide (*see* page 2, paragraphs 20, 21 and 23), and β-sympatico-mimetics, including formoterol and fenoterol (see page 2, paragraphs 36 and 37) for inhalation in the treatment of respiratory passage diseases (*see* page 1, paragraph 7 and page 3, claim 2). The reference teaches the active ingredients can be used singly or in combination. Freund et al. also teach an active agent concentration range of 10mg/100ml to 20000mg/100ml and a nebuliser delivering 12 microliters of concentrate per operation (*see* page 3, paragraph 52). Therefore, the dose of active agent would be between 1.2 mcg and 2400 mcg per operation.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact

was unknown at the time of the prior invention"). Also see *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound "inherently" anticipated the claimed hemihydrate form of the compound because practicing the process in the prior art to manufacture the anhydrous compound "inherently results in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate). In the instant application, Claim 1 recites a functional limitation of "effective therapy for at least 10 hours". The instant specification appears to demonstrate that both aqueous and dry powder formulations of trospium are therapeutically effective for at least 10 hours. Thus it appears that a 10 hour effective duration of action of trospium is independent of its formulation and one would anticipate that the aqueous trospium formulation taught by Freund et al. would have a similar therapeutically effective duration of action, absent evidence to the contrary.

Applicants argue the duration of action of the trospium formulations are dose dependent. Applicants argue the Examiner "must provide a factual basis to reasonably support that the allegedly inherent characteristic necessarily flows from the teachings of the cited reference each and every time; the mere fact that a certain thing may result from a given set of circumstances is simply not sufficient (MPEP §2112; Ex parte Levy, 17 USPQ2d 1461 (Bd. Pat. App. & Inter. 1990); In re Robertson, 169 F.3d. 743, 745 (Fed Cir. 1999)." Applicants point to instant Figure 1b, which demonstrates a relationship between the dose of trospium and duration of action.

The relationship of the dose of trospium to the duration of action is a characteristic of trospium. Since Freund et al. teach a dose range which encompasses the instantly claimed dose range, the duration of action of trospium taught by Freund et al. would be the same as that of the instant invention.

Applicants also argue the "skilled person would not necessarily choose trospium from amongst the list of over 100 drugs named in Freund".

A reference that clearly names the claimed species anticipates the claim no matter how many other species are named. A genus does not always anticipate a claim to a species within the genus.. However, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. *Ex parte* A, 17 USPQ2d 1716 (Bd. Pat. App. & Inter.1990). In instant case, the instantly claimed trospium is disclosed by Freund et al. in a list of 4 anticholinergic agents.

Claim Rejections - 35 USC § 103

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Claims 1, 2, 4, 5, 22-26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freund et al. (*Ibid.*), in view of Richards et al. (U.S. Patent Application Pub. No. 2003/0158176).

The teachings of Freund et al. are presented *supra*.

Freund et al. does not teach specific respiratory passage diseases.

Richards et al. teach anticholinergic (antimuscarinic) agents, including the compound, trospium, are useful for the treatment of acetylcholine-mediated disorders, in particular, the treatment of *inter alia* chronic obstructive pulmonary disease (COPD) and asthma (*see* page 5, paragraphs 91 and 93). Richards et al. teach the advantageous administration of anticholinergic agents by inhalation or insufflation in the form of an aerosol or a dry powder (administered by dry powder inhaler (*see* page 6, paragraphs 103 and 106). Richards et al. teach that dose of anticholinergic agents depends on many factors, including the potency of the compound, the age and weight of the patient and the severity of the condition (*see* page 6, paragraph 105). One of ordinary skill in the art would have optimized the dose taught by Freund et al. to maximize the therapeutic effects and minimize the deleterious effects of the active agent.

One of ordinary skill in the art (e.g., a pulmonologist) would have found it obvious to combine these two teachings to treat diseases such as COPD and asthma by local (i.e., inhalation) administration of trospium and an additional agent, such as formoterol. Freund et al. teach the usefulness of trospium and formoterol for treating respiratory passages diseases and Richards et al. teach COPD and asthma as two respiratory diseases effectively treated by trospium. One would have been motivated to administer the active agents via inhalation to directly target the respiratory system, thereby minimizing the amount of active agents administered systemically, thus avoiding excessive systemic absorption and resulting undesirable systemic effects, and to improve upon the known methods of treatment for COPD and asthma.

Applicants' argue the Office "has still not accounted for the fact that Richards [et al.] simply teaches nothing about dosage or formulation or hours of therapeutic effectiveness of *trospium*" (emphasis by Applicants). Applicants argue the therapeutic effectiveness of the formulations taught by Freund et al. are not tested and that one skilled in the art would not have substituted one anticholinergic agent with another "with a reasonable expectation of therapeutic effectiveness for any time frame based on Freund".

As presented *supra*, Freund et al. teach aqueous aerosols of *inter alia* anticholinergic agents, including trospium chloride and ipratropium bromide, and β-sympatico-mimetics, including formoterol and fenoterol for inhalation in the treatment of respiratory passage diseases. Richards et al. was provided to demonstrate prior art knowledge of the use of anticholinergic agents in the treatment of acetylcholine-mediated disorders and these that these disorders include COPD. With regard to the novel compounds taught by Richards et al., the reference states "[t]he compounds of the invention have anti-cholinergic properties. *Thus, they are useful for the treatment of acetylcholine-mediated disorders*. In particular, they are useful for treating asthma, chronic obstructive pulmonary disease (COPD)…" (emphasis added). See page 5, column 93. This is a teaching that compounds which are anticholinergic agents (not just the novel compounds disclosed by Richards et al.) are useful for acetylcholine-mediated disorders which include COPD. Further, Richards et al. teach prior art knowledge of the anticholinergic properties of trospium. The rejection does not depend upon a teaching by Richards et al. of dosage, formulation or hours of therapeutic effectiveness of

trospium. Richards et al. teach trospium to be an anticholinergic agent and provides ample motivation to the skilled artisan to select trospium (one of 4 anticholinergic agents disclosed by Freund et al.) as an active agent in the Freund et al. reference.

9. Claims 1, 2, 4-8, 10-13, 15, 18-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freund et al. (U.S. Patent Application Pub. No. 2001/0008632), in view of Richards et al. (U.S. Patent Application Pub. No. 2003/0158176) as applied to Claim 1, 2, 4, 5, 22-26 and 28 above, and further in view of Bernstein et al. (U.S. Patent Application Pub. No. 2004/0105821 A1).

Bernstein et al. teach particulate sustained release pharmaceutical formulations for inhalation administration. See Abstract. The sustained release dry powder formulations are disclosed to be useful in the treatment of respiratory disease, including *inter alia* asthma and COPD. Further, the sustained release formulation provides local or plasma concentrations at nearly constant values over the intended period of release (for example, up to 2 to 24 hours), allowing patients to take treatments once or twice daily. See page 13, paragraphs 184, 189 and 190. Bernstein et al. teach anticholinergic agents (such as ipratropium bromide) and bronchodilator/sympathimetic agents (such as formoterol) may be formulated by the methods disclosed. See pages 8-9, paragraphs 92 and 123. Although Bernstein et al. do not teach trospium *per se*, they do teach anticholinergic agents in general. Freund et al. also teach anticholinergic agents can be administered by dry powder formulation, as well as specifically teaching both ipratropium bromide and trospium. One of ordinary skill in the art at the time of the invention would have understood (especially in light of the teaching of Freund et al.) that

one known anticholinergic agent (i.e., trospium) could be substituted for another (i.e., ipratropium) with a reasonable expectation of success. The formulations disclosed by the reference utilize spray drying techniques. See page 10, paragraph 148, and page 11, paragraphs 159-162. The aerodynamic diameter of the formulation is adjusted to enable particle deposition by inhalation to the region of interest in the lung. See pages 4-5, paragraphs 44 and 52. Particles taught by Bernstein et al. have a volume average diameter and volume median diameter of between 1 and 5 microns, and a tap densities ranging from 0.22 to 0.68 g/mL, and at least 50% by weight of the microparticles delivered to the lung is delivered to the central and upper lung; these disclosures satisfy the requirements of instant Claims 8, 9, 11, and 12. See page 5, paragraph 57; page 14, Table 1; and page 15-16, claims 4, 5 and 21. The reference teaches the inclusion of surfactants (e.g., lipids), including phospholipids and bulking agents (e.g., amino acids), including leucine, in the formulations. See page 2, paragraph 14; page 6, paragraph 68; page 10, paragraphs 143 and 144; and pages 15-16, claims 10 and 31. The surfactants comprise less than 10% by weight of the microparticles and 0.1 to 5% of the formulation. See page 7, paragraph 79 and page 12, paragraph 171. The active pharmaceutical agent is present from about 5 to 50 wt %. See page 9, paragraph 138. One would presume the remainder of the formulation (i.e., about 45—90 wt %) would by comprised of the bulking agent (e.g., leucine).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the above 3 references to create an effective treatment for respiratory diseases, such as COPD, that was administered by inhalation to target the

lungs and reduce undesirable systemic effects, and long lasting so as to allow for once daily administration. The reference to Freund et al. and Richards et al. teach suitable therapeutic agents and routes of administration and Bernstein et al. teach methods for creating sustained release formulations of active agents suitable for treating respiratory conditions, including COPD. One would have been motivated to do so to improve upon the known methods of treatment for these respiratory diseases.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants argue Bernstein et al. “is directed to particle formulation and does not provide any evidence of the therapeutic effectiveness of any [of] the hundreds of therapeutic agents listed therein”. Further, Applicants assert that “Bernstein [et al.] provides no information or evidence with regard to the therapeutic effectiveness or hours of therapeutic effectiveness of the formulations or whether such formulations actually provide the extended release properties asserted in Bernstein [et al.]".

As discussed *supra*, the reference to Bernstein et al. was provided for their teaching of particulate sustained release pharmaceutical formulations for inhalation administration; that sustained release dry powder formulations are useful in the treatment of respiratory disease, including *inter alia* asthma and COPD; and sustained release formulations to provide local or plasma concentrations at nearly constant values over the intended period of release, providing an extended duration of action. Bernstein et al. teach anticholinergic agents (such as ipratropium bromide) and bronchodilator/sympathimetic agents (such as formoterol) may be formulated by the methods disclosed, and, although Bernstein et al. do not teach trospium *per se*, they do teach anticholinergic agents in general.

Conclusion

10. Claims 1, 2, 4-8, 10-16, and 18-28 are rejected.

11. No claims are allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GREGG POLANSKY whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614